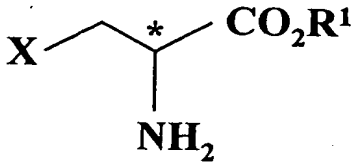
Claims

1. A process for producing an optically active N-protected-aziridine-2-carboxylic acid represented by the following formula (3):

(3)

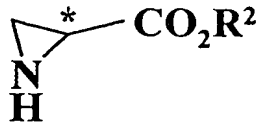
wherein * represents the position of an asymmetric carbon atom; and P^1 represents a benzenesulfonyl group substituted by nitro at the 2- and/or 4-positions;
or its salt characterized by comprising subjecting an optically active 3-haloalanine derivative represented by the following formula (1):



(1)

wherein X represents a halogen atom; R^1 represents a hydrogen atom or a monovalent organic group which is involved in a structure represented by $-CO_2R^1$ and thus is capable of serving as an ester type protective group of a carboxyl group; and * is as defined above;
to an intramolecular cyclization reaction in the presence of a base followed by, if needed, ester hydrolysis to give

an optically active aziridine-2-carboxylic acid derivative represented by the following formula (2):



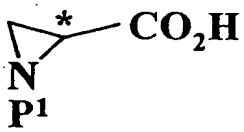
(2)

wherein * is as defined above; and R^2 has the same meaning as R^1 as defined above;
or its salt while maintaining the configuration at the 2-position, and then protecting the amino group followed by, if needed, ester hydrolysis.

2. The production process as claimed in claim 1, wherein P^1 in the formula (3) is a 2-nitrobenzenesulfonyl group or a 4-nitrobenzenesulfonyl group.

3. A production process as claimed in claim 1 or 2, wherein X in the formula (1) is a chlorine atom.

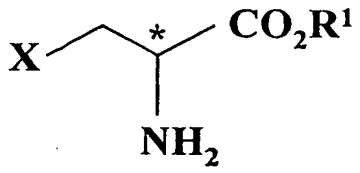
4. A process for producing an optically active N-protected-aziridine-2-carboxylic acid represented by the following formula (3):



(3)

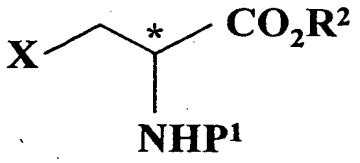
wherein P^1 and * are each as defined above;

or its salt characterized by protecting the amino group of an optically active 3-haloalanine derivative represented by the following formula (1):



(1)

wherein X, R^1 and * are each as defined above;
or its salt followed by, if needed, ester hydrolysis to give an optically active N-protected-3-haloalanine derivative represented by the following formula (4):



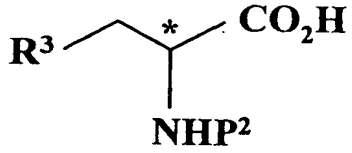
(4)

wherein X and * are each as defined above; R^2 has the same meaning as R^1 as defined above; and P^1 is the same as P^1 in the above formula (3);
or its salt, then subjecting it to an intramolecular cyclization reaction in the presence of a base followed by, if needed, ester hydrolysis.

5. The production process as claimed in claim 4, wherein X in the formula (1) is a chlorine atom.

6. A production process as claimed in claim 4 or 5, wherein P^1 in the formula (4) is a 2-nitrobenzenesulfonyl group or a 4-nitrobenzenesulfonyl group.

7. A process for producing an optically active amino acid derivative represented by the following formula (6):



(6)

wherein R^3 represents an optionally substituted cyclic or noncyclic alkyl group having 1 to 30 carbon atoms, an optionally substituted aralkyl group having 7 to 30 carbon atoms, an optionally substituted aryl group having 6 to 30 carbon atoms, an optionally substituted alkenyl group having 2 to 30 carbon atoms, or an optionally substituted alkynyl group having 2 to 30 carbon atoms; and P^2 has the same meaning as P^1 as described above or represents a hydrogen atom;

or its salt characterized by comprising treating an optically active N-protected-aziridine-2-carboxylic acid represented by the following formula (3) which is produced by a method as claimed in any of claims 1 to 6:

(3)

wherein P^1 and * are each as defined above;

or its salt with an organic metal reagent represented by the following formula (5):

$$R^3M \qquad (5)$$

wherein R^3 is as defined above; and M represents an atomic group containing an alkali metal atom or an alkaline earth metal atom or an atomic group containing a zinc ion;

followed by, if needed, deblocking.

8. The production process as claimed in claim 7, wherein M in the formula (5) is lithium, sodium, MgCl, MgBr, ZnCl or ZnBr.

9. A production process as claimed in claim 7 or 8, wherein said deblocking is performed with the use of a thiol compound represented by the following formula (7):

$$R^4SH \qquad (7)$$

wherein R^4 represents an optionally substituted alkyl group having 1 to 30 carbon atoms, an optionally substituted aralkyl group having 7 to 30 carbon atoms, or an optionally substituted aryl group having 6 to 30 carbon atoms;

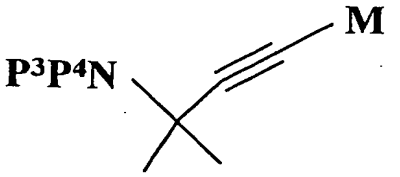
to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

10. The production process as claimed in claim 9, wherein said thiol compound represented by the formula (7) is thiophenol.

11. A production process as claimed in claim 7 or 8, wherein said deblocking is performed with the use of a metal alkoxide to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

12. The production process as claimed in claim 11, wherein said metal alkoxide is an alkali metal alkoxide.

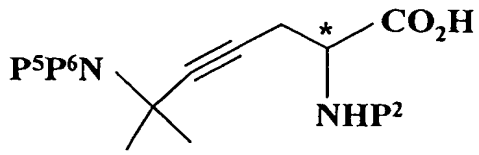
13. A production process as claimed in any of claims 7 to 12, wherein a metal acetylide represented by the following formula (8):



(8)

wherein M is as defined above; and P^3 and P^4 independently represent each a hydrogen atom or an amino-protective group, or P^3 and P^4 form together an amino-protective group;

is used as said organic metal reagent represented by the formula (5) to give an optically active amino acid derivative represented by the following formula (9):

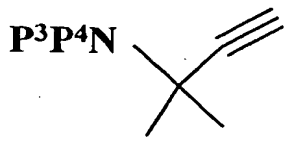


(9)

wherein P^5 and P^6 independently have the same meanings as P^3 and P^4 as described above; P^2 has the same meaning as P^2 as defined in the above formula (6); and * represents the position of an asymmetric carbon atom;

or its salt as the compound represented by the formula (6).

14. The production process as claimed in claim 13, wherein said metal acetylide represented by the formula (8) is prepared by treating an optionally protected 3,3-dimethylpropargylamine represented by the following formula (10):



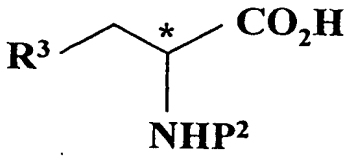
(10)

wherein P^3 and P^4 are each as defined above;

with at least one member selected from among organic lithium, organic lithium amide, a Grignard reagent and organic magnesium amide.

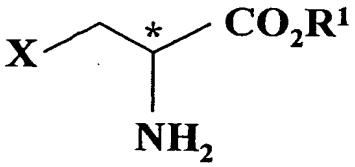
15. A production process as claimed in claim 13 or 14, wherein P^3 and P^4 in the formulae (8) and (10) respectively represent a hydrogen atom and a benzyl group.

16. A process for producing an optically active amino acid derivative represented by the following formula (6):



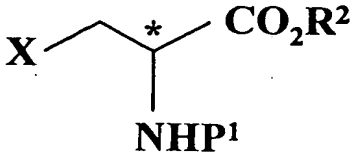
(6)

wherein R^3 and P^2 are each as defined above;
or its salt characterized by comprising protecting the amino group of an optically active 3-haloalanine derivative represented by the following formula (1):



(1)

wherein X, R^1, * are each as defined above;
or its salt followed by, if needed, ester hydrolysis to give an optically active N-protected-3-haloalanine derivative represented by the following formula (4):



(4)

wherein X, R^2 and * are each as defined above;
or its salt, and then treating it with an organic metal reagent represented by the following formula (5):

$$R^3M \qquad (5)$$

wherein R^3 is as defined above;

followed by, if needed, deblocking and/or ester hydrolysis.

17. The production process as claimed in claim 16, wherein X in the formula (1) is a chlorine atom.

18. A production process as claimed in claim 16 or 17, wherein M in the formula (5) is lithium, sodium, MgCl, MgBr, ZnCl or Zn Br.

19. A production process as claimed in any of claims 16 to 18, wherein said deblocking is performed with the use of a thiol compound represented by the following formula (7):

$$R^4SH \qquad (7)$$

wherein R^4 is as defined above;

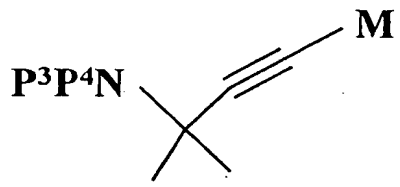
to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

20. The production process as claimed in claim 19, wherein said thiol compound represented by the formula (7) is thiophenol.

21. A production process as claimed in any of claims 16 to 18, wherein said deblocking is performed with the use of a metal alkoxide to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

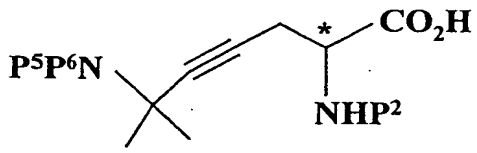
22. The production process as claimed in claim 21, wherein said metal alkoxide is an alkali metal alkoxide.

23. A production process as claimed in any of claims 16 to 22, wherein a metal acetylide represented by the following formula (8):



(8)

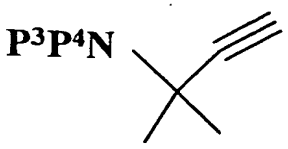
wherein M, P^3 and P^4 are each as defined above;
is used as said organic metal reagent represented by the formula (5) to give an optically active amino acid derivative represented by the following formula (9):



(9)

wherein P^2, P^5, P^6 and * are each as defined above;
or its salt as the compound represented by the formula (6).

24. The production process as claimed in claim 23, wherein said metal acetylide represented by the formula (8) is prepared by treating an optionally protected 3,3-dimethylpropargylamine represented by the following formula (10):

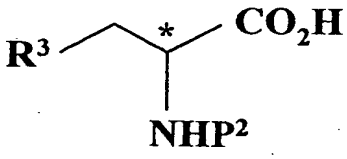


(10)

wherein P^3 and P^4 are each as defined above;
with at least one member selected from among organic lithium, organic lithium amide, a Grignard reagent and organic magnesium amide.

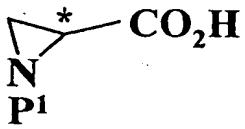
25. A production process as claimed in claim 23 or 24, wherein P^3 and P^4 in the formula (8) respectively represent a hydrogen atom and a benzyl group.

26. A process for producing an optically active amino acid derivative represented by the following formula (6):



(6)

wherein R^3, P^2 and * are each as defined above;
or its salt characterized by comprising treating an optically active N-protected aziridine-2-carboxylic acid represented by the following formula (3):



(3)

wherein P^1 and * are each as defined above;

or its salt with an organic metal reagent represented by the following formula (5):

$$R^3M \qquad (5)$$

wherein R^3 and M are each as defined above;

followed by, if needed, deblocking.

27. The production process as claimed in claim 26, wherein M in the formula (5) is lithium, sodium, MgCl, MgBr, ZnCl or ZnBr.

28. A production process as claimed in claim 26 or 27, wherein said deblocking is performed with the use of a thiol compound represented by the following formula (7):

$$R^4SH \qquad (7)$$

wherein R^4 is as defined above;

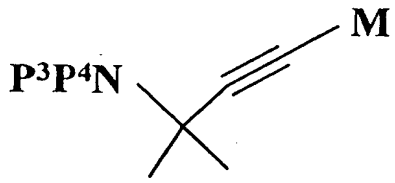
to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

29. The production process as claimed in claim 28, wherein said thiol compound represented by the formula (7) is thiophenol.

30. A production process as claimed in claim 26 or 27, wherein said deblocking is performed with the use of a metal alkoxide to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

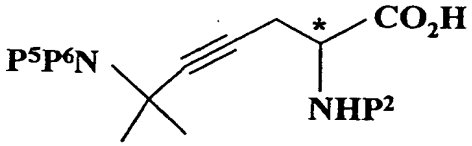
31. The production process as claimed in claim 30, wherein said metal alkoxide is an alkali metal alkoxide.

32. A production process as claimed in any of claims 26 to 31, wherein a metal acetylide represented by the following formula (8):



(8)

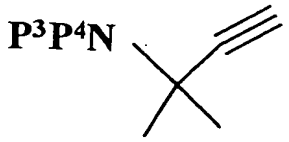
wherein M, P^3 and P^4 are each as defined above;
is used as said organic metal reagent represented by the formula (5) to give an optically active amino acid derivative represented by the following formula (9):



(9)

wherein P^2, P^5, P^6 and * are each as defined above;
or its salt as the compound represented by the formula (6).

33. The production process as claimed in claim 32, wherein said metal acetylide represented by the formula (8) is prepared by treating an optionally protected 3,3-dimethylpropargylamine represented by the following formula (10):

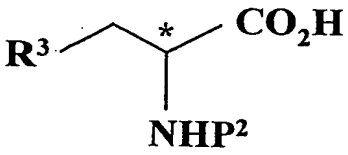


(10)

wherein P^3 and P^4 are each as defined above;
with at least one member selected from among organic lithium, organic lithium amide, a Grignard reagent and organic magnesium amide.

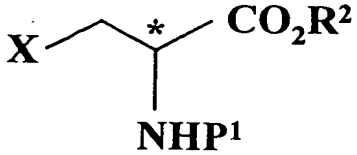
34. A production process as claimed in claim 32 or 33, wherein P^3 and P^4 in the formula (8) respectively represent a hydrogen atom and a benzyl group.

35. A process for producing an optically active amino acid derivative represented by the following formula (6):



(6)

wherein R^3 and P^2 are each as defined above;
or its salt characterized by comprising treating an optically active N-protected-3-haloalanine derivative represented by the following formula (4):



(4)

wherein X, R^2, P^1 and * are each as defined above;

or its salt with an organic metal reagent represented by the following formula (5):

$$R^3M \qquad (5)$$

wherein R^3 and M are each as defined above;
followed by, if needed, deblocking and/or ester hydrolysis.

36. The production process as claimed in claim 35, wherein X in the formula (4) is a chlorine atom.

37. A production process as claimed in claim 35 or 36, wherein M in the formula (5) is lithium, sodium, MgCl, MgBr, ZnCl or Zn Br.

38. A production process as claimed in any of claims 35 to 37, wherein said deblocking is performed with the use of a thiol compound represented by the following formula (7):

$$R^4SH \qquad (7)$$

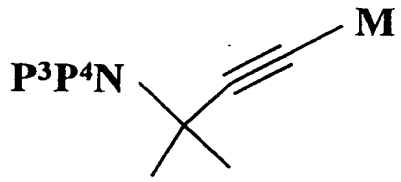
wherein R^4 is as defined above;
to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

39. The production process as claimed in claim 38, wherein said thiol compound represented by the formula (7) is thiophenol.

40. A production process as claimed in any of claims 35 to 37, wherein said deblocking is performed with the use of a metal alkoxide to give a compound represented by the formula (6) wherein P^2 is a hydrogen atom.

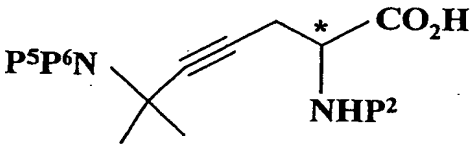
41. The production process as claimed in claim 40, wherein said metal alkoxide is an alkali metal alkoxide.

42. A production process as claimed in any of claims 35 to 41, wherein a metal acetylide represented by the following formula (8):



(8)

wherein M, P^3 and P^4 are each as defined above;
is used as said organic metal reagent represented by the formula (5) to give an optically active amino acid derivative represented by the following formula (9):



(9)

wherein P^2, P^5, P^6 and * are each as defined above;
or its salt as the compound represented by the formula (6).

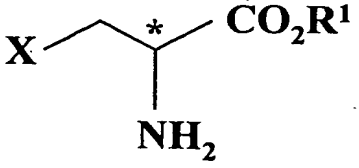
43. The production process as claimed in claim 23, wherein said metal acetylide represented by the formula (8) is prepared by treating an optionally protected 3,3-dimethylpropargylamine represented by the following formula (10):

(10)

wherein P^3 and P^4 are each as defined above;
with at least one member selected from among organic lithium, organic lithium amide, a Grignard reagent and organic magnesium amide.

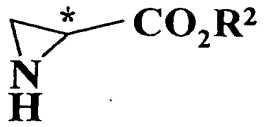
44. A production process as claimed in claim 42 or 43, wherein P^3 and P^4 in the formula (8) respectively represent a hydrogen atom and a benzyl group.

45. A process for producing an optically active aziridine-2-carboxylic acid derivative or its salt which comprises using an optically active 3-haloalanine derivative represented by the following formula (1):



(1)

wherein X, R^1 and * are each as defined above;
or its salt in the presence of a base to give an optically active aziridine-2-carboxylic acid derivative represented by the following formula (2):



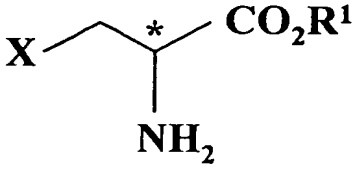
(2)

wherein R^2 and * are each as defined above;
or its salt, characterized by, using an alkali metal hydroxide or an alkaline earth metal hydroxide as the base, performing an intramolecular cyclization reaction in the presence of water at a temperature of 70°C or higher followed by, if needed, ester hydrolysis.

46. The production process as claimed in claim 45, wherein said base is an alkali metal hydroxide.

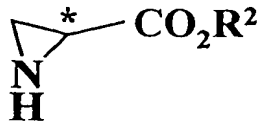
47. A production process as claimed in claim 45 or 46, wherein said optically active 3-haloalanine derivative or its salt is added to a mixture containing water and a base.

48. A process for producing an optically active aziridine-2-carboxylic acid derivative or its salt which comprises using an optically active 3-haloalanine derivative represented by the following formula (1):



(1)

wherein X, R^1 and * are each as defined above;
or its salt in the presence of a base to give an optically active aziridine-2-carboxylic acid derivative represented by the following formula (2):



(2)

wherein R^2 and * are each as defined above;
or its salt, characterized by, using an amine as the base, performing an intramolecular cyclization reaction followed by, if needed, ester hydrolysis.

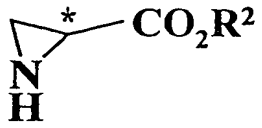
49. The production process as claimed in claim 48, wherein said amine is an aliphatic amine.

50. A process for producing an optically active N-protected-aziridine-2-carboxylic acid represented by the following formula (3):

(3)

wherein P^1 and * are each as defined above;
or its salt characterized by comprising treating an optically active aziridine-2-carboxylic acid derivative

represented by the following formula (2) which is produced by a method as claimed in any of claims 45 to 49:



(2)

wherein R^2 and * are each as defined above;
with benzenesulfonyl chloride p substituted by nitro at the 2- and/or 4-positions followed by, if needed, ester hydrolysis.

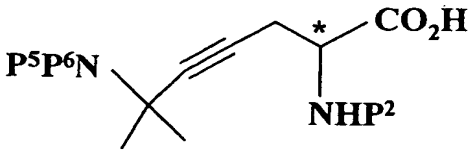
51. An optically active N-protected-aziridine-2-carboxylic acid represented by the following formula (3):

(3)

wherein P^1 and * are each as defined above;
or its salt.

52. A compound as claimed in claim 51, wherein P^1 is a 2-nitrobenzenesulfonyl group or a 4-nitrobenzenesulfonyl group.

53. An optically active amino acid derivative represented by the following formula (9):



(9)

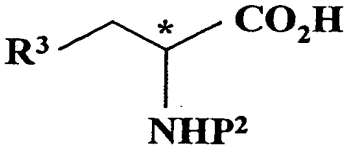
wherein P^2, P^5, P^6 and * are each as defined above;
or its salt.

54. A compound as claimed in claim 53, wherein P^2 is a 2-nitrobenzenesulfonyl group or a 4-nitrobenzenesulfonyl group.

55. A compound as claimed in claim 53, wherein P^2 is a hydrogen atom.

56. A compound as claimed in any of claims 53 to 55, wherein P^5 is a hydrogen atom and P^6 is a benzyl group.

57. A process for crystallizing a compound represented by the following formula (6):



(6)

wherein R^3 is as defined above;
characterized by comprising neutralizing with an acid an aqueous solution containing an N-protected optically active amino acid derivative salt represented by the formula (6) wherein P^2 is a 2-nitrobenzenesulfonyl group or a 4-nitrobenzenesulfonyl group and thus crystallizing to thereby give the compound of the formula (6) in free state.

58. The crystallization process as claimed in claim 57, wherein said N-protected amino acid derivative salt is an alkali metal salt.

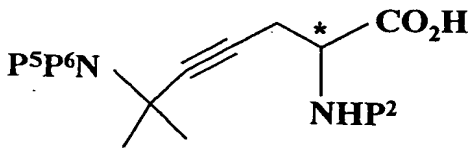
59. The crystallization process as claimed in claim 58, wherein said alkali metal salt is a lithium salt.

60. A crystallization process as claimed in any of claims 57 to 59, wherein said acid is a halogenated hydroacid.

61. The crystallization process as claimed in claim 60, wherein said halogenated hydroacid is hydrogen chloride.

62. A crystallization process as claimed in any of claims 57 to 61, wherein the reaction is performed in the coexistence of an organic solvent compatible with water.

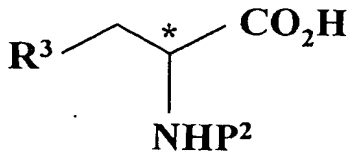
63. A crystallization process as claimed in any of claims 57 to 62, wherein said compound represented by the formula (6) is an N-protected optically active amino acid derivative salt represented by the following formula (9):



(9)

wherein P^2 represents a 2-nitrobenzenesulfonyl group or a 4-nitrobenzenesulfonyl group; and P^5, P^6 and * are each as defined above.

64. A process for crystallizing a compound represented by the following formula (6):



(6)

wherein R^3 is as defined above;

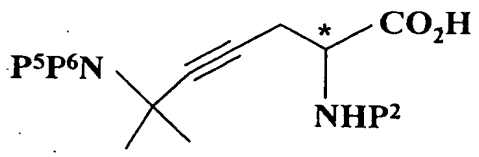
characterized by comprising salting out with a halogenated alkali metal salt an aqueous solution containing an alkali metal salt of an optically active amino acid derivative represented by the formula (6) wherein P^2 is hydrogen atom to thereby give an alkali metal salt of the compound (6).

65. The crystallization process as claimed in claim 64, wherein said alkali metal salt of an optically active amino acid derivative is a lithium salt.

66. A crystallization process as claimed in claim 64 or 65, wherein said halogenated alkali metal salt is lithium chloride.

67. A crystallization process as claimed in any of claims 64 to 66, wherein the reaction is performed in the coexistence of an organic solvent compatible with water.

68. A crystallization process as claimed in any of claims 64 to 67, wherein said compound represented by the formula (6) is an optically active amino acid derivative salt represented by the following formula (9):



(9)

wherein P^2 represents a hydrogen atom; and P^5, P^6 and * are each as defined above.